

**FPIES (Enterocolitis inducida por proteínas de la dieta),  
una entidad no solo de la edad pediátrica**

**Purificación González Delgado**

**S. Alergia Hospital General Universitario de Alicante  
Dr. Balmis**

# Alergia Alimentos

Incremento patología desencadenada por alimentos

20% adultos se autodiagnostican como alérgicos a alimentos (prevalencia real: 3-7%):



## Dietas innecesarias

Pérdida tolerancia, aumento riesgo reacciones IgE mediadas previamente toleradas.

# Adverse reactions to foods

Immune mediated

Non-immune mediated

Toxic reactions

**Food allergy**

**Food intolerance**

**Toxins**  
Bacterial toxins  
Aflatoxins  
Scombroid poisoning

Pathophysiology explained    unexplained

## **IgE-mediated**

Urticaria  
Angioedema  
Bronchospasm  
Rhinitis  
Laryngospasm  
Diarrhoea/  
vomiting  
Anaphylaxis  
Oral Allergy

## **Non-IgE-mediated**

Food protein  
-induced  
enterocolitis  
syndrome  
Food protein  
-induced  
proctocolitis  
Food protein  
-induced  
enteropathies

## **Mixed IgE- and non-IgE-mediated**

Cow's Milk Protein  
Allergy  
Eosinophilic  
Oesophagitis  
Eosinophilic  
Gastroenteritis

**Coeliac  
Disease**

## **Pharmacological**

caffeine  
tyramine

## **Enzyme deficiencies**

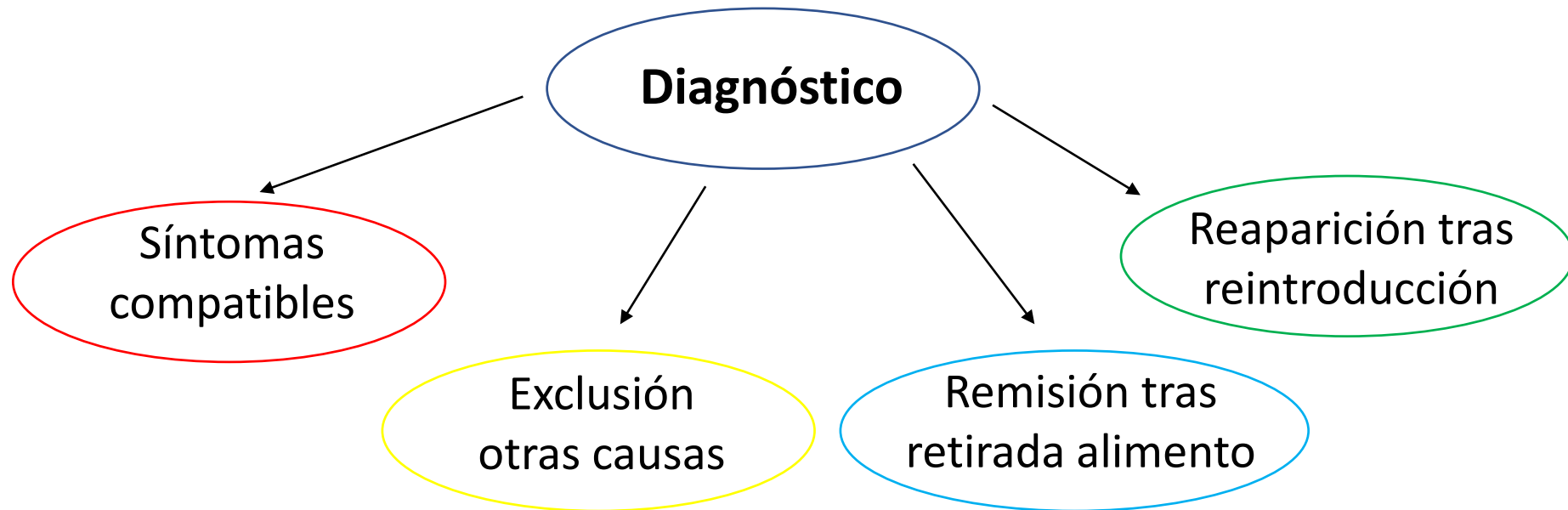
lactose/  
fructose  
malabsorption

## **Non specific gut and non-gut reactions to food**

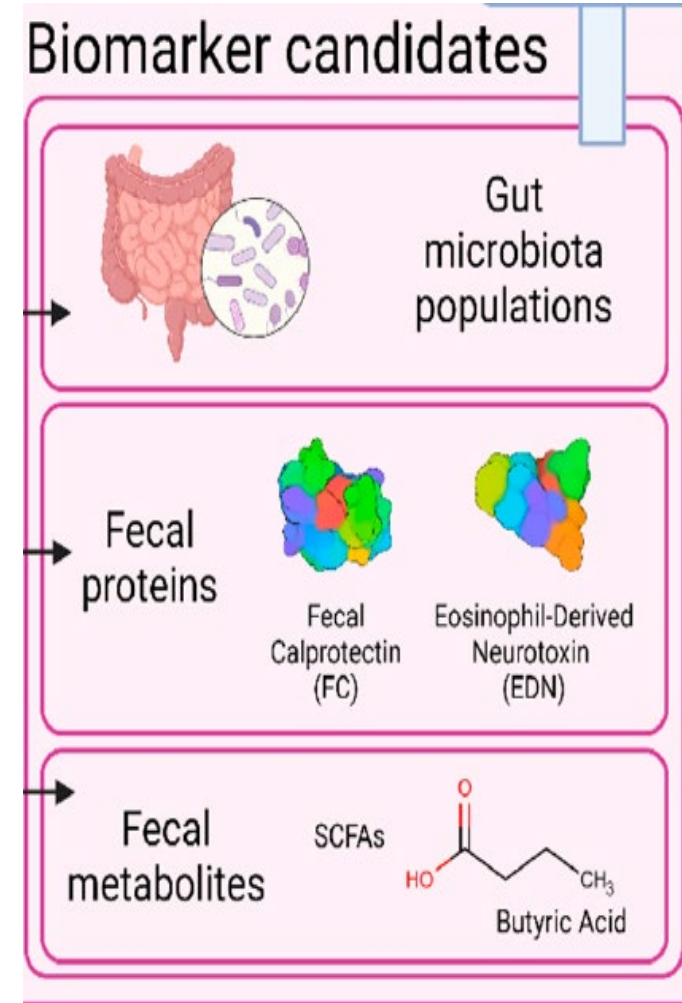
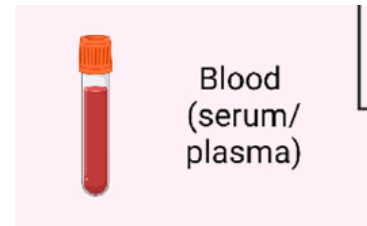
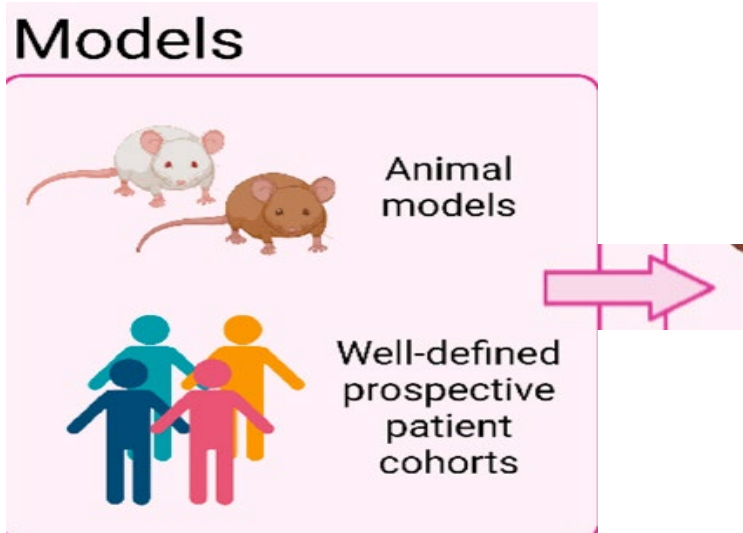
includes Irritable Bowel  
Syndrome & other functional  
GI disorders:  
-luminal distension  
-heightened gastrocolic reflex  
-altered perception  
Behavioural factors:  
-expectation/conditioning  
Psychological factors

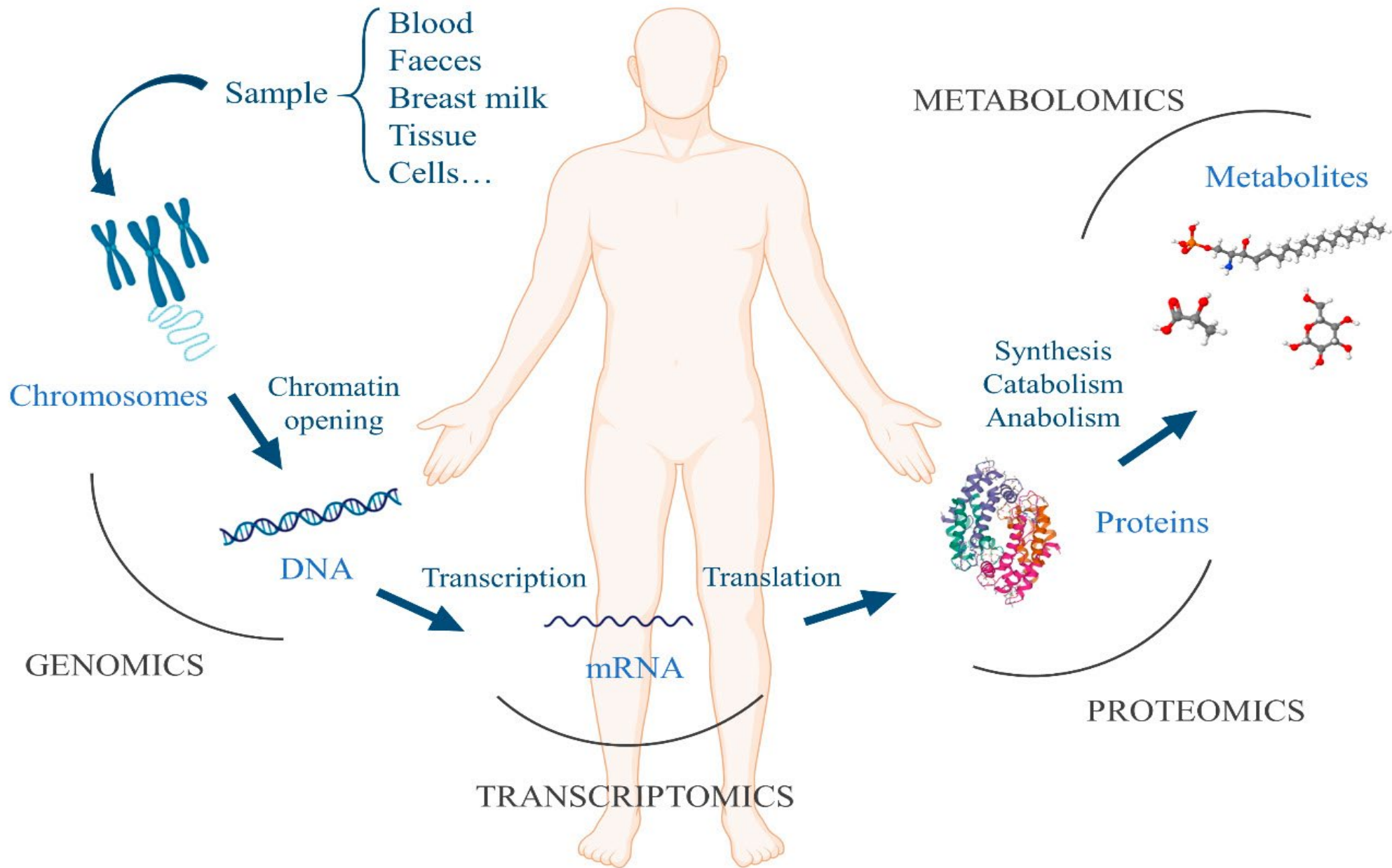
# Alergia Alimentos No-IgE mediada

- Prevalencia aún desconocida: %??



# Diagnóstico Alergia Alimentos no-IgE mediada





# FPIES (Enterocolitis inducida por proteínas dieta)

**Primeros casos: Años 70**



**Año 2016, ICD-10 K52.22  
Estudios epidemiológicos**



**2017: Consenso Internacional FPIES**

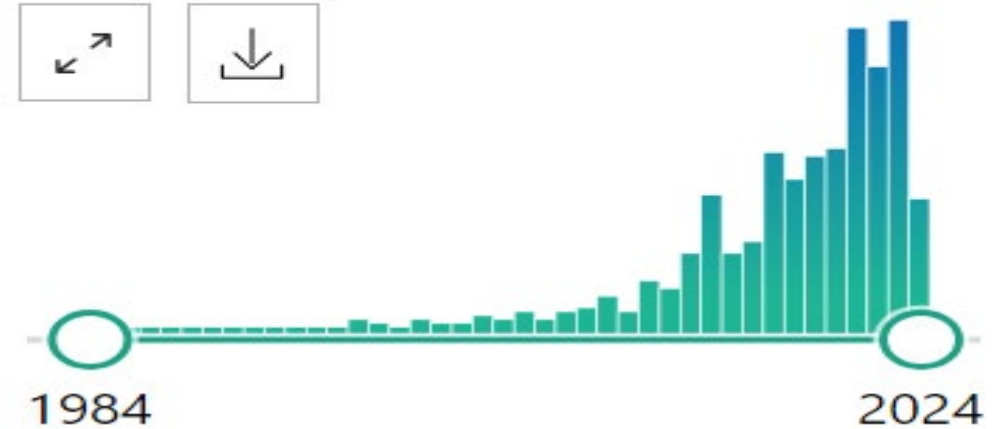


**Criterios diagnósticos y fenotipos**



**Gran interés últimos años**

RESULTS BY YEAR



# FPIES agudo. Definición



- **Alergia no IgE mediada**
- **Vómitos** repetitivos, 1-4 h post-ingesta, letargo, palidez, hipotermia, hipotensión, acidemia (shock like)
- ¿Típica en la infancia?
- **Infradiagnóstico**
  - Ausencia síntomas respiratorios, cutáneos
  - P. latencia (hrs.)
  - Alimentos atípicos



**International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology**

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Anna Nowak-Węgrzyn, MD, Mirna Chehade, MD, Marion E. Groetch, MS, RDN, Jonathan M. Spergel, MD, PhD, Robert A. Wood, MD, Katrina Allen, MD, PhD, Dan Atkins, MD, Sami Bahna, MD, PhD, Ashis V. Barad, MD, Cecilia Berin, PhD, Terri Brown Whitehorn, MD, A. Wesley Burks, MD, Jean-Christoph Caubet, MD, Antonella Cianferoni, MD, PhD, Marisa Conte, MLIS, Carla Davis, MD, Alessandro Fiocchi, MD, Kate Grimshaw, PhD, RD, RNutr, Ruchi Gupta, MD, Brittany Hofmeister, RD, J. B. Hwang, MD, Yitzhak Katz, MD, George N. Konstantinou, MD, PhD, MSc, Stephanie A. Leonard, MD, Jennifer Lightdale, MD, Sean McGhee, MD, Sami Mehr, MD, FRACP, Stefano Miceli Sopo, MD, Giovanni Monti, MD, PhD, Antonella Muraro, MD, PhD, Stacey Katherine Noel, MD, Ichiro Nomura, MD, Sally Noone, RN, MSN, Hugh A. Sampson, MD, Fallon Schultz, MSW, LCSW, CAM, Scott H. Sicherer, MD, Cecilia C. Thompson, MD, Paul J. Turner, MD, Carina Venter, RD, PhD, A. Amity Westcott-Chavez, MA, MFA, and Matthew Greenhawt, MD, MBA, MSc

**International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology**



**1** Major criterion



**≥3** Minor criteria

Vomiting in 1-4 hrs & absence of skin and respiratory sx

- >1 episode to the same food
- Repetitive emesis to another food
- Lethargy
- Pallor
- Emergency room visit
- Need for intravenous fluids
- Diarrhea in 24 hours (5-10 hours)
- Hypotension
- Hypothermia

## Food protein-induced enterocolitis syndrome can occur in adults

*To the Editor:*

A 53-year-old man was referred to our center following 2 episodes of diarrhea and vomiting (in 2008 and 2011), which occurred approximately 4 hours after eating scallops (Mollusca: Bivalvia: Pectinidae). The patient reported a further similar episode occurring more than 20 years ago, with symptoms starting approximately 2 hours after eating clams (Mollusca: Bivalvia). We estimated that in 2008 he ingested ~60 g and in

## Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults

Ju Ann Tan, MBBS<sup>a</sup>, and

William B. Smith, MBBS (Hons), PhD<sup>b</sup>

### *Clinical Implications*

- A distinct syndrome of acute non-IgE-mediated food hypersensitivity, which manifests with isolated gastrointestinal symptoms, has been observed to occur in the adult population. This has some features in common with infantile food protein-induced enterocolitis syndrome, but in adults, it is an acquired condition.
- Features include predominant sensitivity to seafood or egg and a female preponderance.

FPIES EN ADULTOS



## FPIES Adultos

<b>Fernandes et al. (2012)</b>	<b>1 adulto – navajas (bivalvo)</b>
<b>Tan et al. (Australia, 2014)</b>	31 Hipersensibilidad digestiva Adultos, <b>diversos alimentos</b>
<b>Gleich ( USA, 2016)</b>	8 Pacientes , <b>marisco</b>
<b>González-Delgado et al. ( España,2019)</b>	21 Pacientes, <b>pescado y marisco</b>
<b>Du et al. (Canadá, 2019)</b>	20 Pacientes, <b>diversos alimentos</b>
<b>Li et al. ( USA, (2020)</b>	19 Pacientes, <b>marisco</b>
<b>Crespo et al (España, 2021)</b>	25 Pacientes, <b>pescado marisco, verduras</b>
<b>Garcia –Paz (España,2022)</b>	28 Pacientes, <b>pescado, marisco</b>
<b>Crespo (España2022)</b>	42 Pacientes, <b>diversos alimentos</b>
<b>Gonzalez-Delgado et al. (España,2022)</b>	107 Pacientes, <b>diversos alimentos</b>
<b>Huang et al ( USA, 2024)</b>	55 Pacientes, <b>marisco, huevo , pescado</b>
<b>Gonzalez-Delgado (España 2024)</b>	30 pacientes ( <b>huevo</b> )

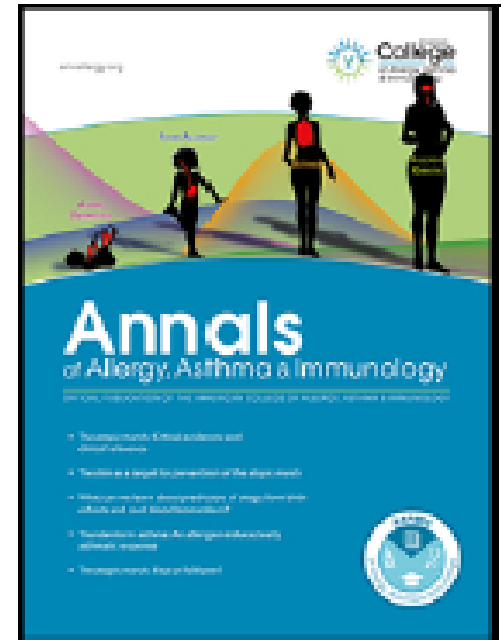
# Food Protein Induced Enterocolitis Syndrome: Not Just in Children

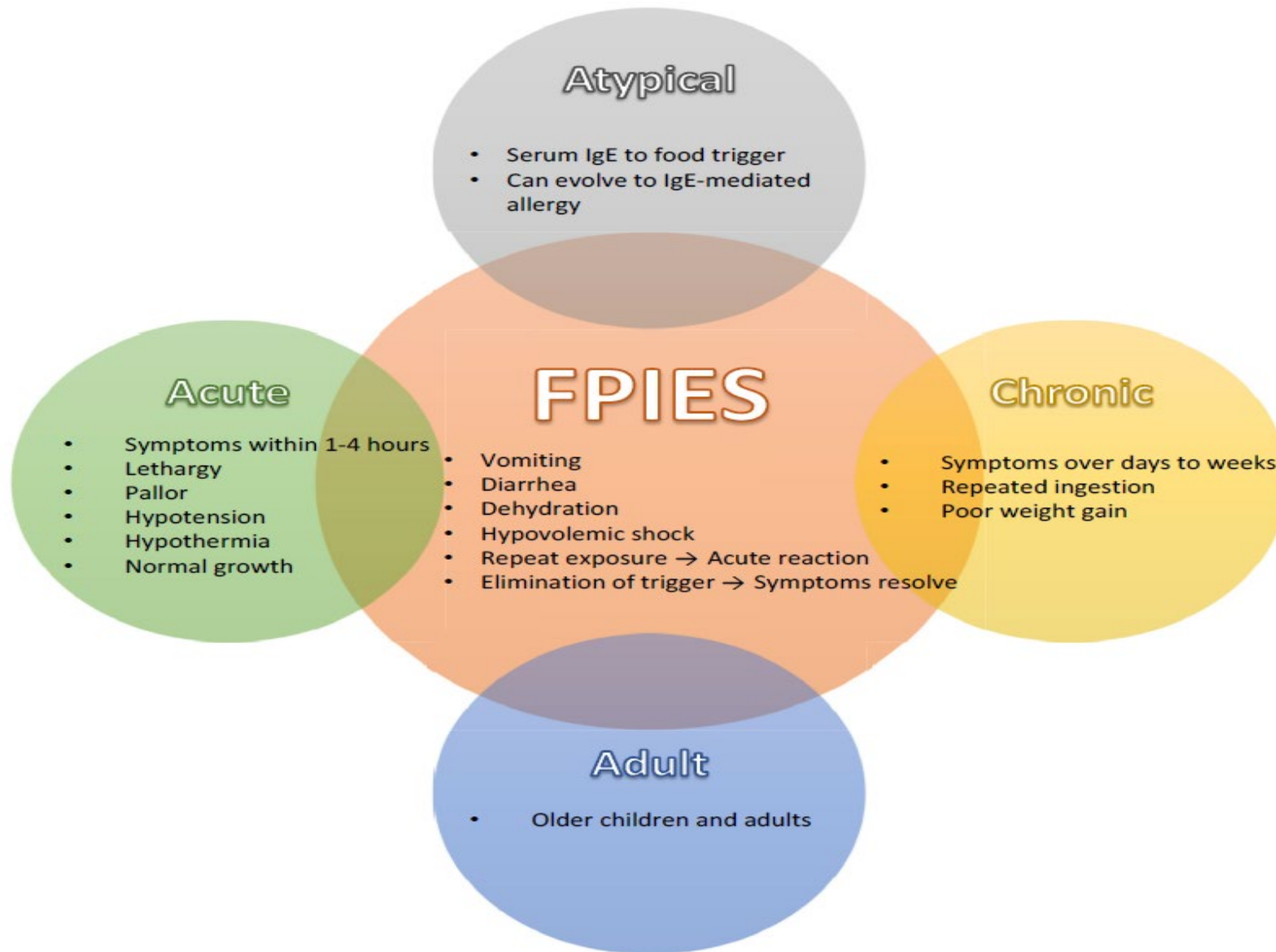
Y. Du BMSc , P. Gonzalez-Delgado MD , P. Vadas MD

PII: S1081-1206(21)00419-1

DOI: <https://doi.org/10.1016/j.anai.2021.05.029>

Reference: ANAI 3622



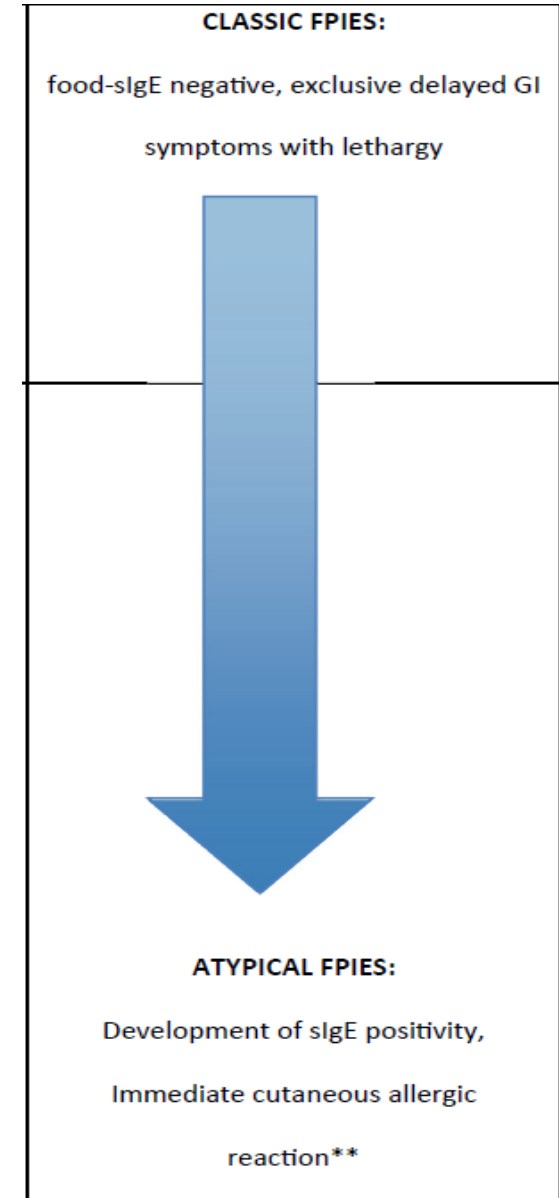


## FPIES atípico

20% presenta IgE específica

-Peor pronóstico ??????

-Evolución a síntomas IgE-mediados ????





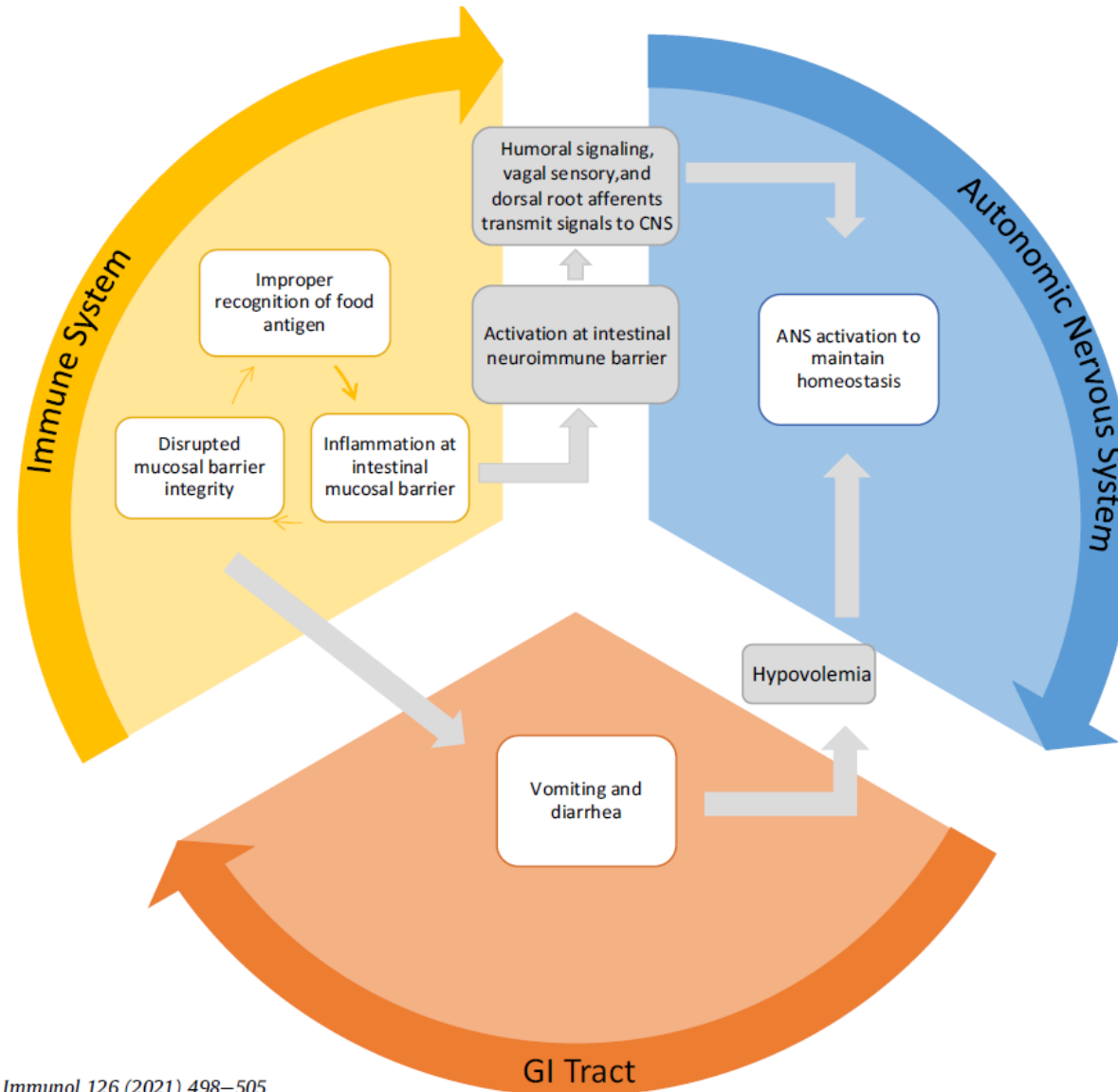
# Prevalencia adultos FPIES

**EEUU**  
Encuesta población, n=53.575.  
Prevalencia: **Adultos 0.22%**



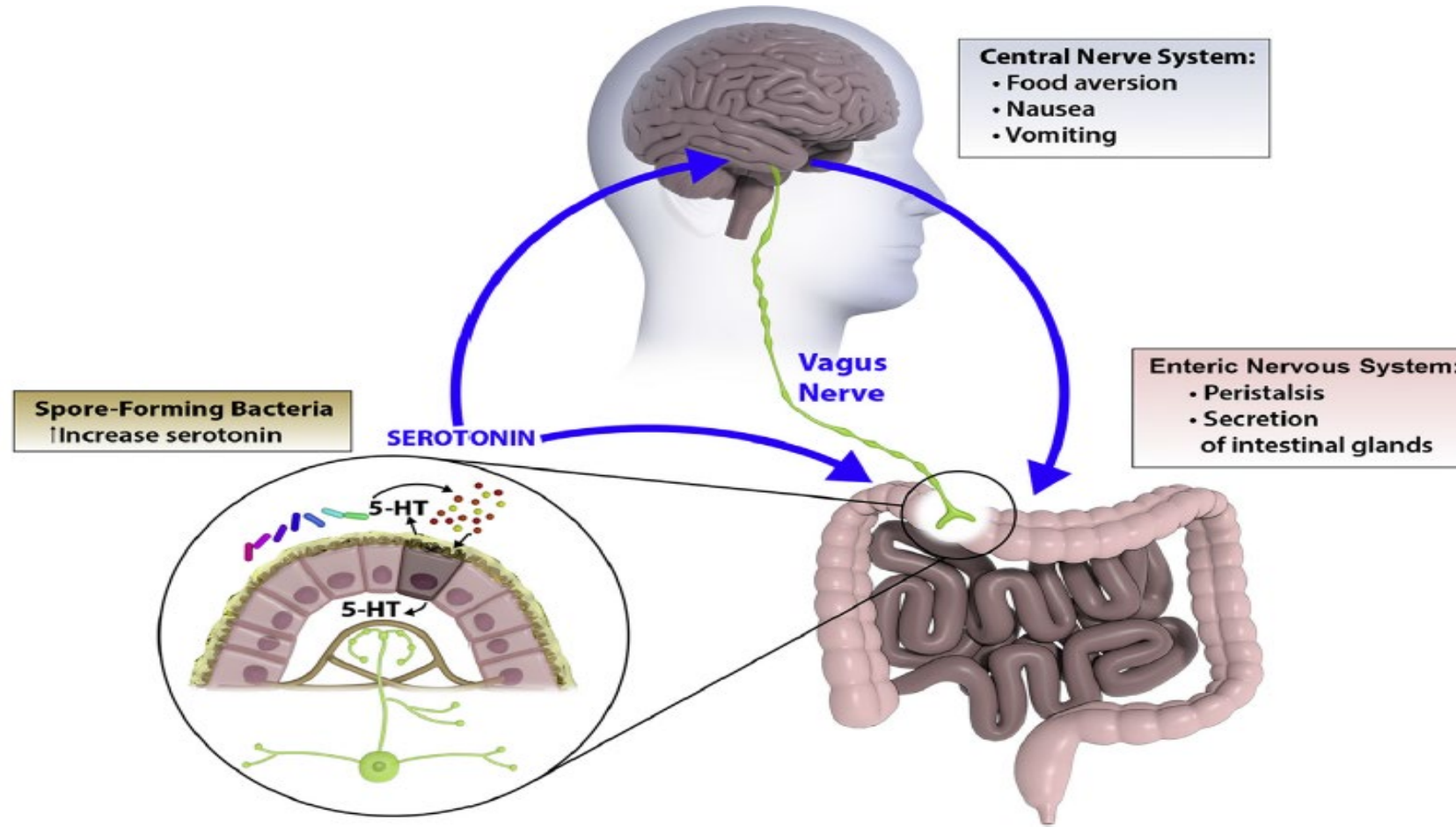
Nowak-Wegrzyn A, Warren CM, Brown-Whitehorn T, Cianferoni A, Schultz-Matney F, Gupta RS. Food protein-induced enterocolitis syndrome in the US population-based study. *J Allergy Clin Immunol.* (2019) 144:1128–30. doi: 10.1016/j.jaci.2019.06.032

# Fisiopatología



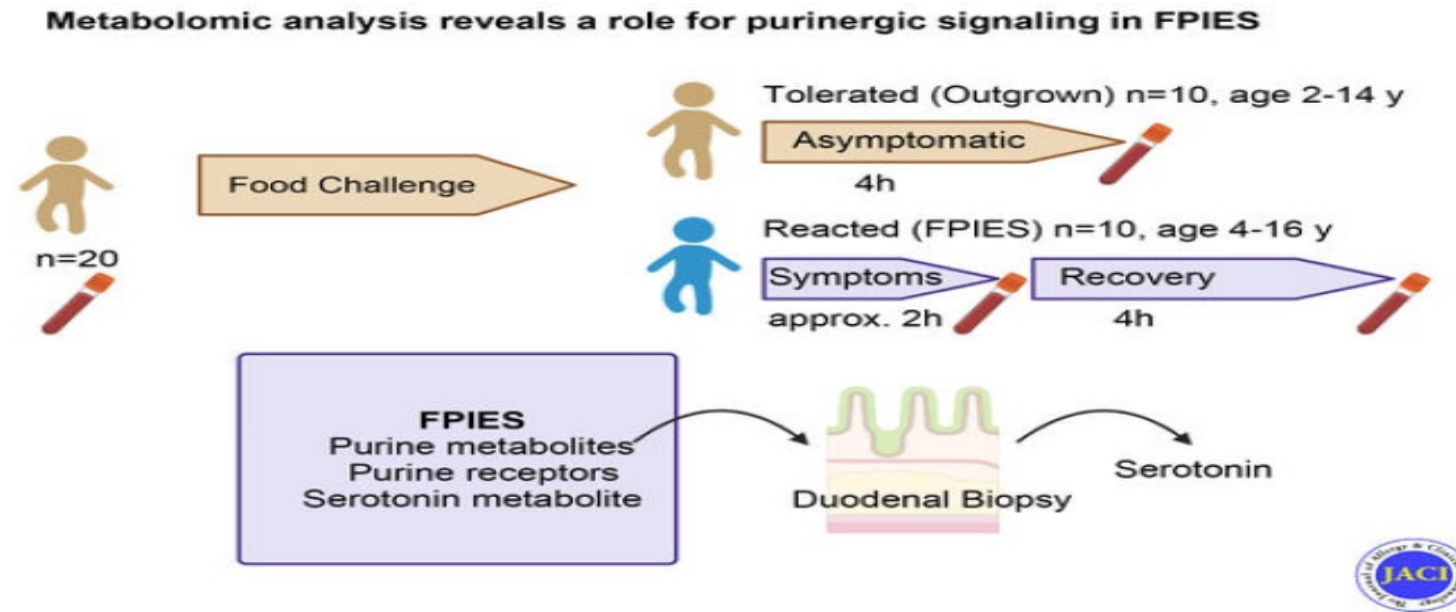
# Gastrointestinal immunopathology of food protein–induced enterocolitis syndrome and other non-immunoglobulin E–mediated food allergic diseases

Kuan-Wen Su, MD<sup>\*,†</sup>; Wayne G. Shreffler, MD, PhD<sup>‡,§,||</sup>; Qian Yuan, MD, PhD<sup>‡,||,¶</sup>



# Untargeted serum metabolomic analysis reveals a role for purinergic signaling in FPIES.

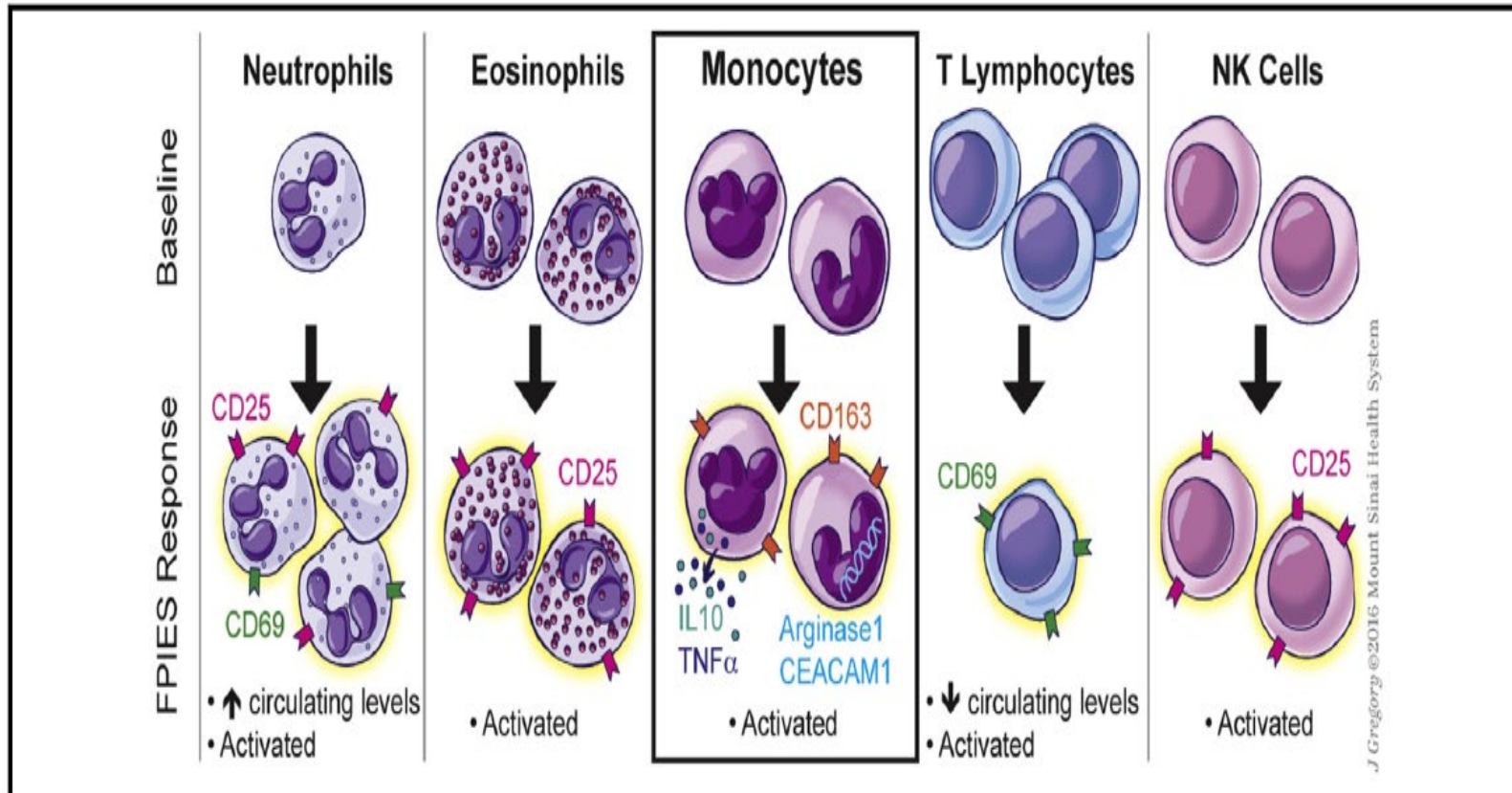
J Allergy Clin Immunol. 2023 March ; 151(3): 797–802. doi:10.1016/j.jaci.2022.09.035



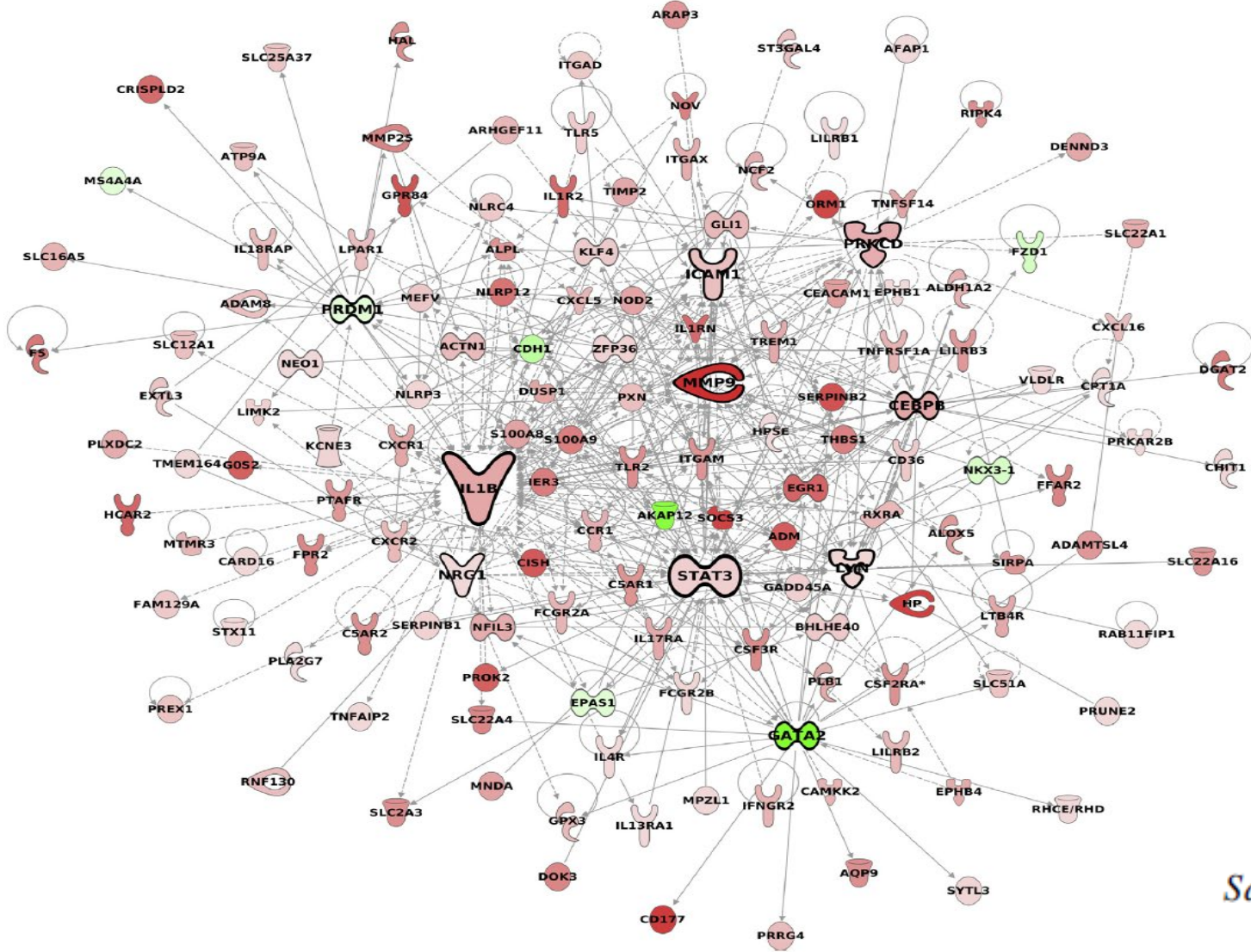
Activation of the purinergic pathway during FPIES reactions provides a possible mechanism connecting inflammation and vomiting symptoms by triggering serotonin release from gastric and duodenal mucosa

# Systemic innate immune activation in food protein-induced enterocolitis syndrome

Ritobrata Goswami, PhD,<sup>a</sup> Ana Belen Blazquez, PhD,<sup>a</sup> Roman Kosoy, PhD,<sup>b</sup> Adeeb Rahman, PhD,<sup>c</sup> Anna Nowak-Węgrzyn, MD, PhD,<sup>a</sup> and M. Cecilia Berin, PhD<sup>a</sup> *New York, NY*



# Innate immune activation occurs in acute food protein-induced enterocolitis syndrome reactions

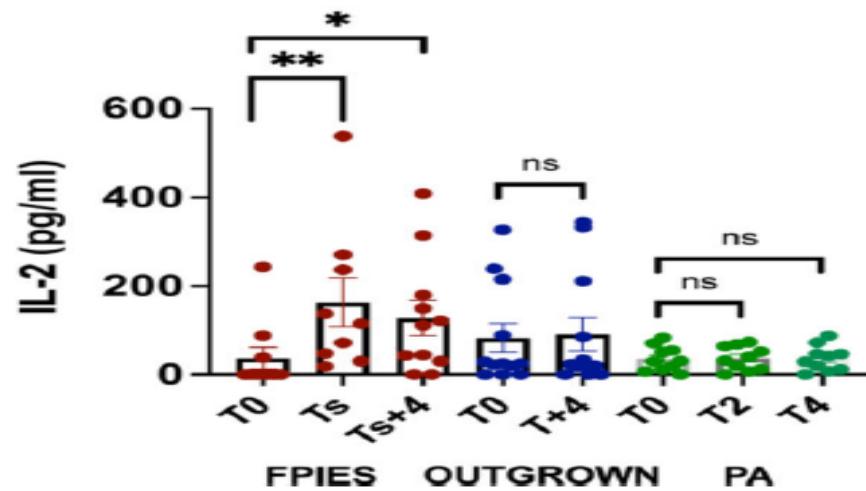
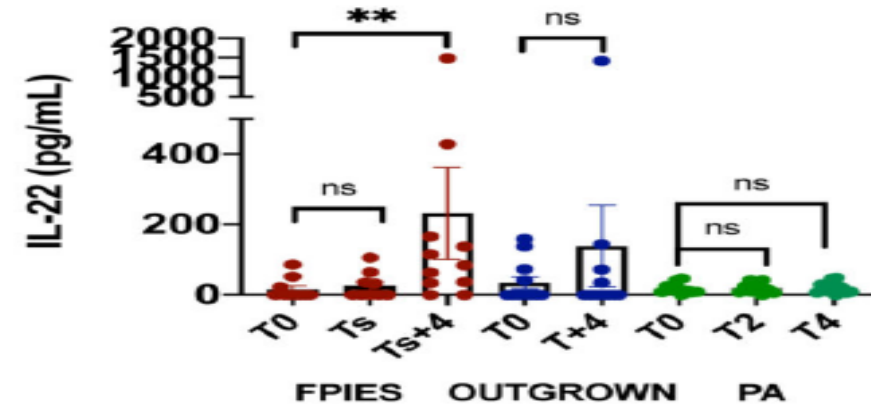
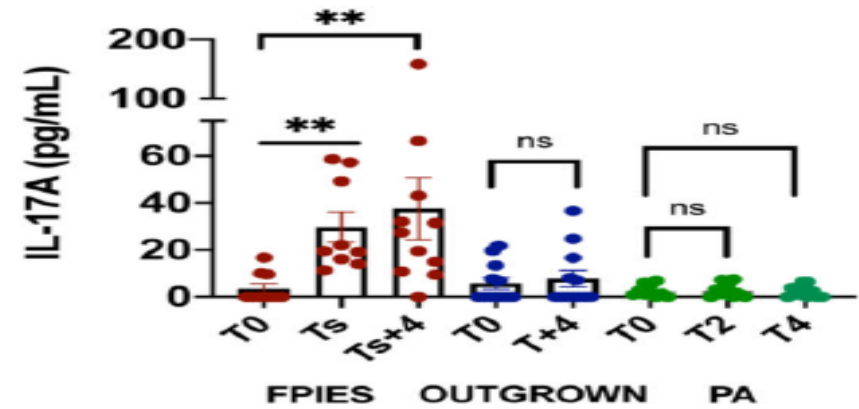


Sam Mehr, MBBS, BMedSci, FRACP, FRCPA<sup>a</sup>  
 Eric Lee, MBBS, BSci<sup>a,b</sup>  
 Peter Hsu, MBBS, FRACP, PhD<sup>a,b</sup>

# Acute FPIES reactions are associated with an IL-17 inflammatory signature

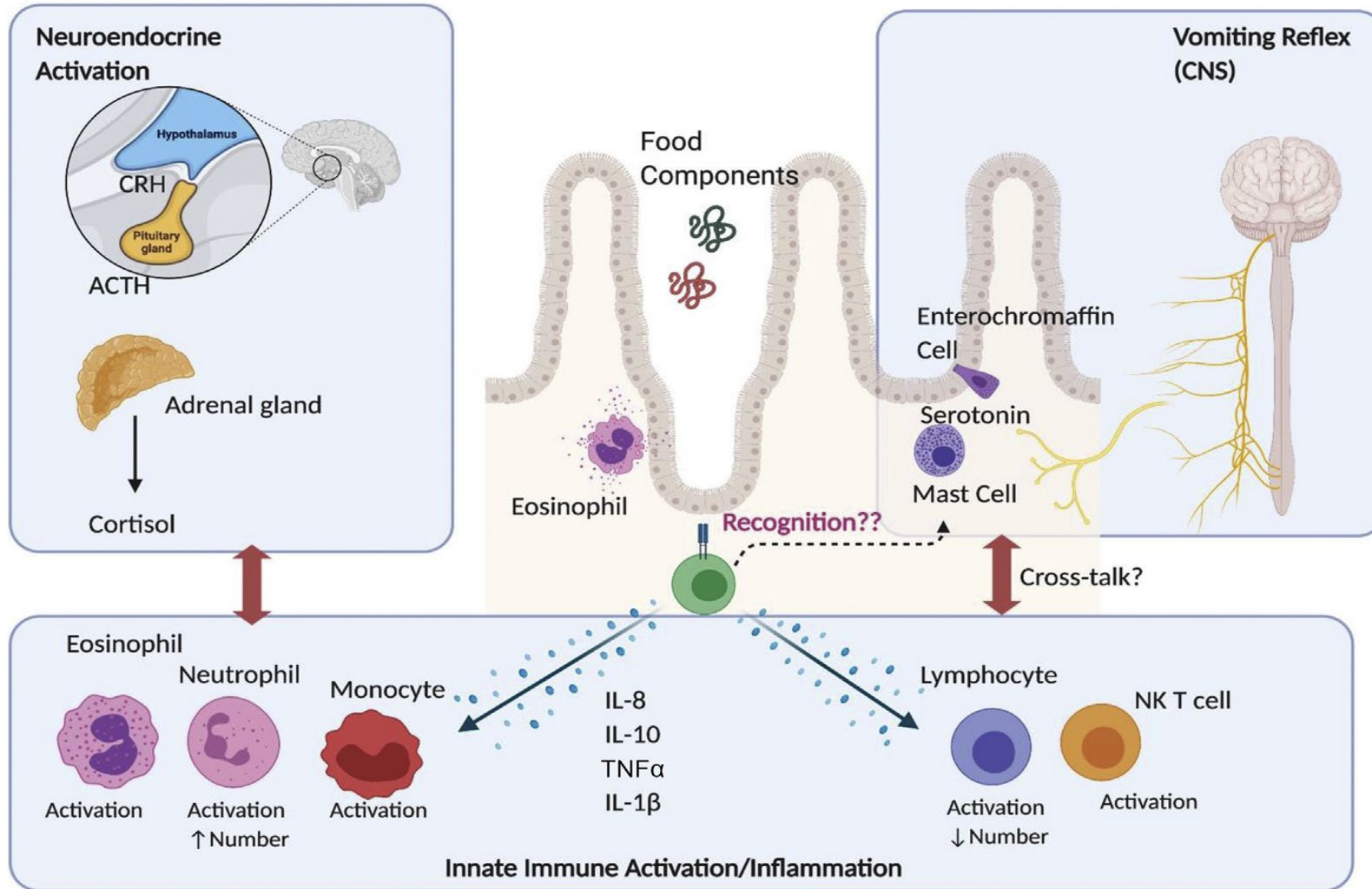
*J Allergy Clin Immunol.* 2021 September ; 148(3): 895–901.e6. doi:10.1016/j.jaci.2021.04.012.

M. Cecilia Berin, PhD<sup>1</sup>, Daniel Lozano-Ojalvo, PhD<sup>1</sup>, Charuta Agashe, MS<sup>1</sup>, Mary Grace Baker, MD<sup>1</sup>, J. Andrew Bird, MD<sup>2</sup>, Anna Nowak-Wegrzyn, MD, PhD<sup>3,4</sup>



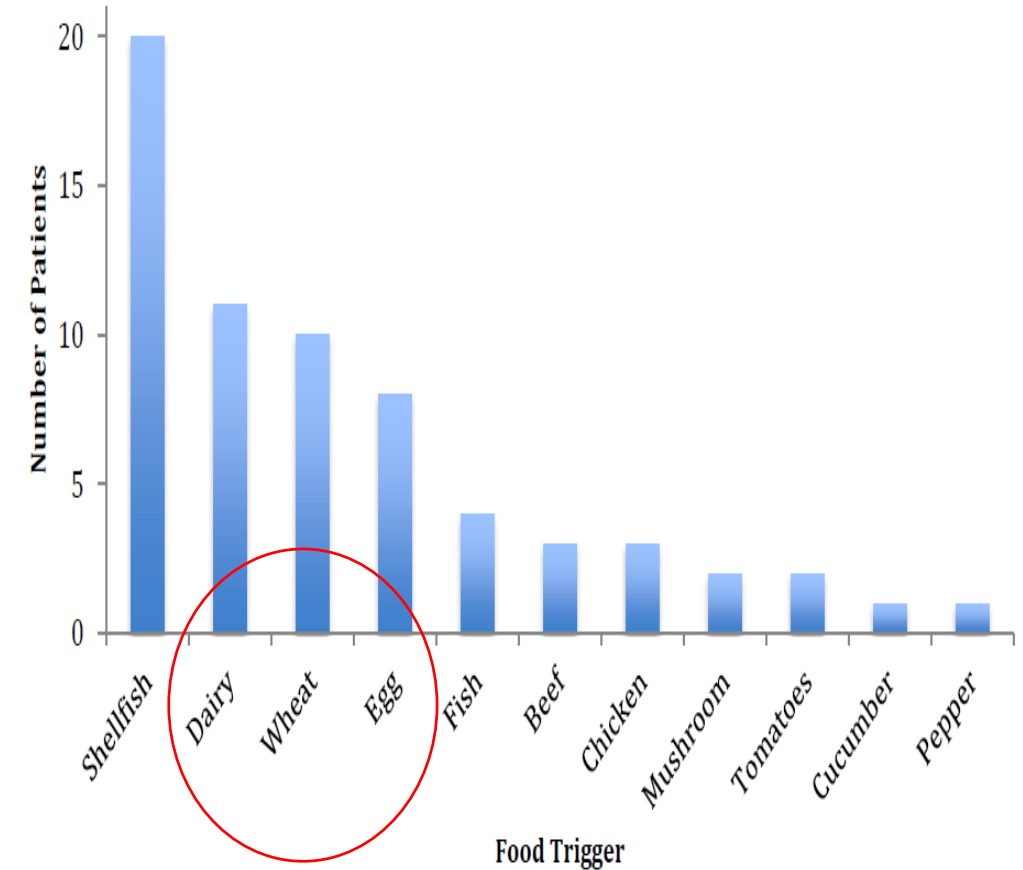
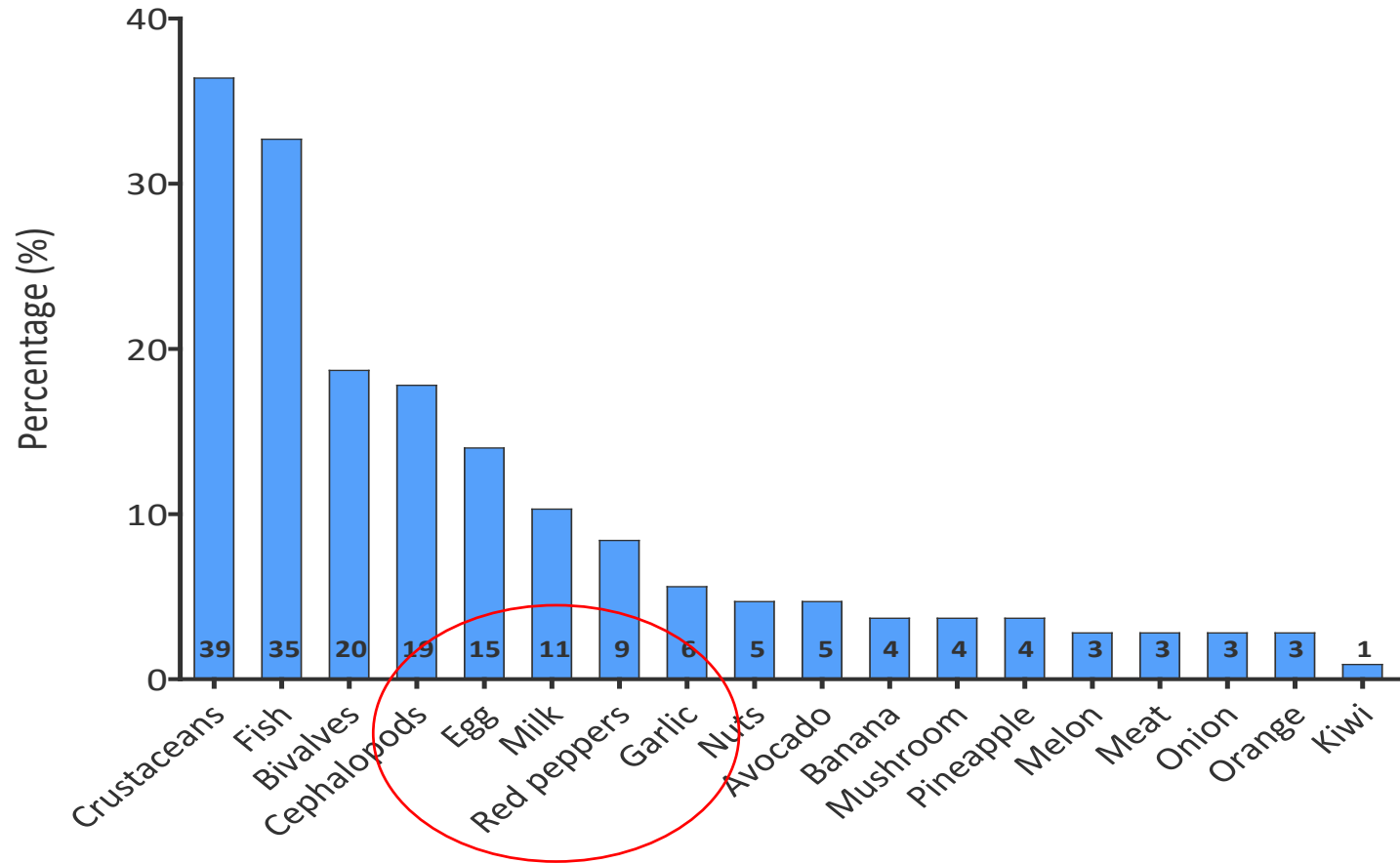
# Advances in understanding immune mechanisms of food protein-induced enterocolitis syndrome

M.C. Berin / Ann Allergy Asthma Immunol 126 (2021) 478e481





# Alimentos implicados en Fpies del adulto



## **Food Protein-Induced Enterocolitis Syndrome in Adulthood: Clinical Characteristics, Prognosis, and Risk Factors.**

P. González-Delgado, MD, et al **J Allergy Clin Immunol Pract** 2022;10:239

Yue (Jennifer) Du , Anna Nowak-Węgrzyn , Peter Vadas , FPIES in Adults,

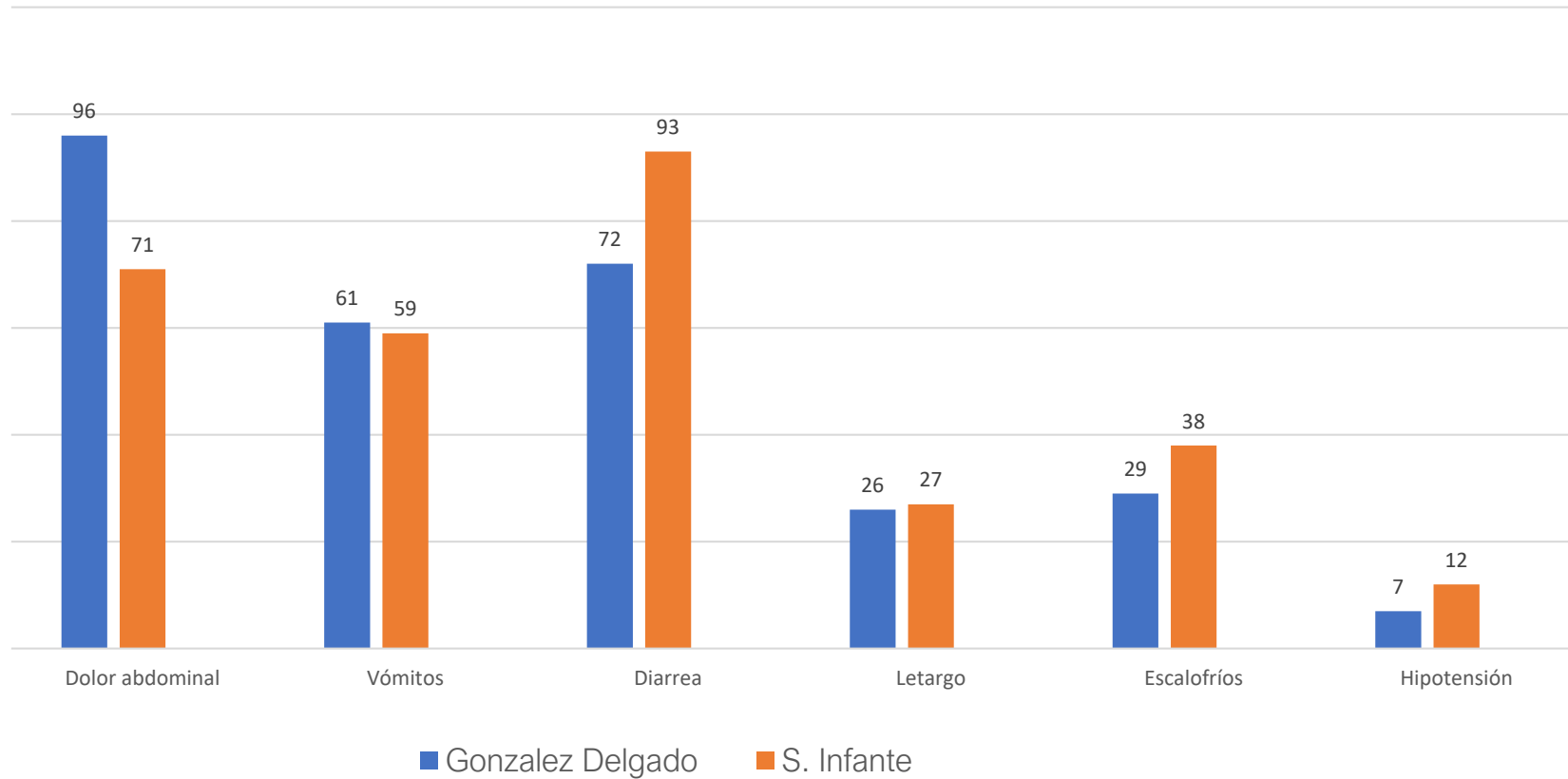
*Annals of Allergy, Asthma Immunology* (2018), doi: <https://doi.org/10.1016/j.anai.2018.08.001>

# FPIES Adultos

RESULTS	
Men	7 (6.7%)
Women	100 (93.3%)
Age at first reaction, years Median (IQ 25-75)	30 (23.4)
Delay to diagnosis, years Median (IQ 25-75)	4 (2-10)
Nº episodes, median (IQ 25-75)	8 (5-10)
Latency period, min Median (IQ 25-75)	120 (50-240)
Duration symptoms, h Median (IQ 25-75)	9 (5.7-10.5)
Emergency department	15 (14%)
Atopy	70(65.4%)

**Food Protein-Induced Enterocolitis Syndrome in Adulthood: Clinical Characteristics, Prognosis, and Risk Factors. J Allergy Clin Immunol Pract 2022;10:2397** P. González-Delgado, MD, PhD, J. Muriel, PhD, T. Jiménez, MD, PhD, J I. Cameo, PhD, A Palazón-Bru, PhD, and J Fernández, MD, PhD, Alicante, Spain

# Síntomas FPIES adulto



# FPIES INICIO EDAD ADULTA

**1** Major criterion



**>3** Minor criteria

~~Vomiting in 1-4 hrs  
& absence of skin  
and respiratory sxS~~

>1 episode to the same food

Repetitive emesis to another food

Lethargy

Pallor

Emergency room visit

Need for intravenous fluids

Diarrhea in 24 hours (5-10 hours)

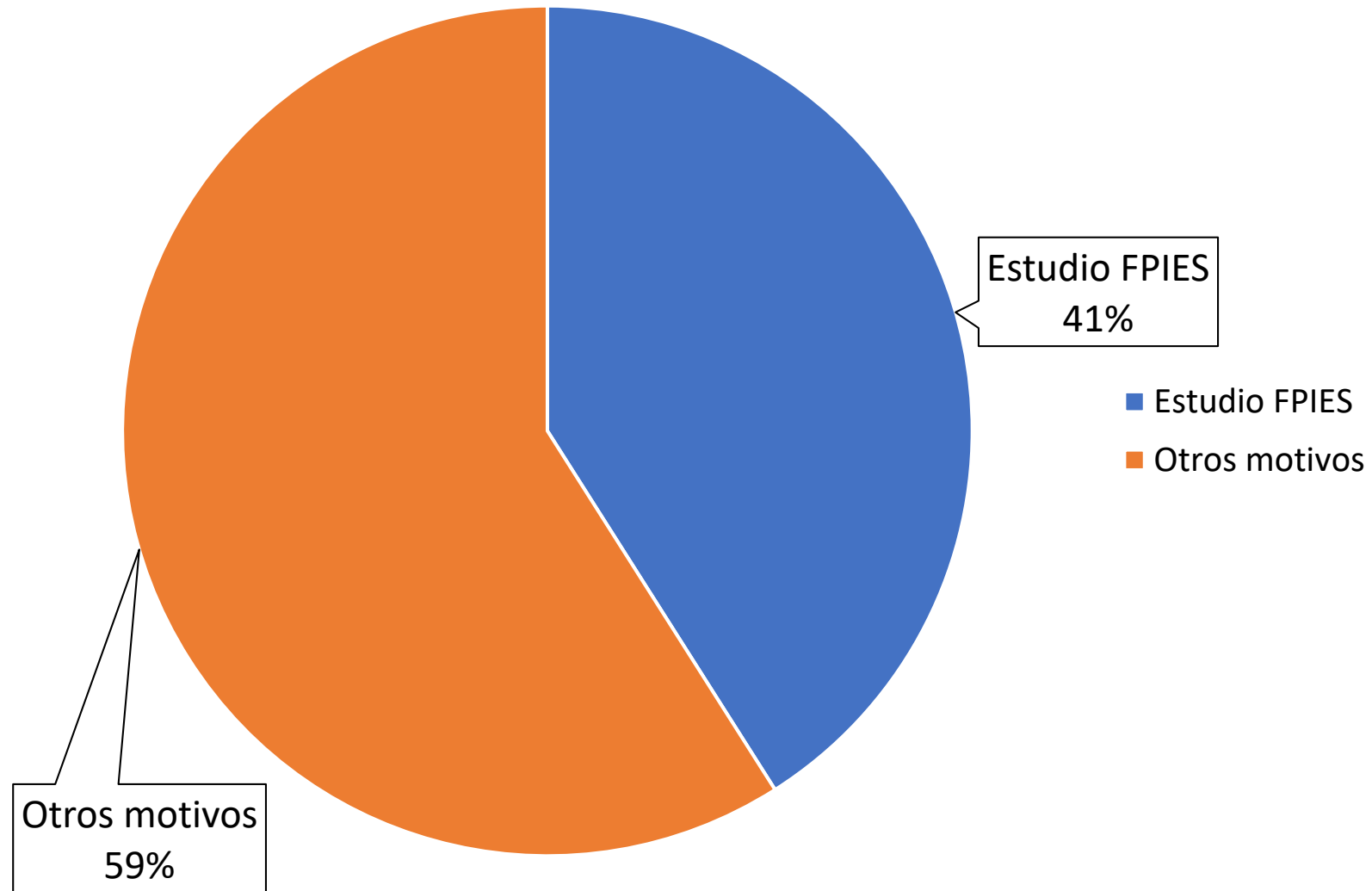
Hypotension

Hypothermia



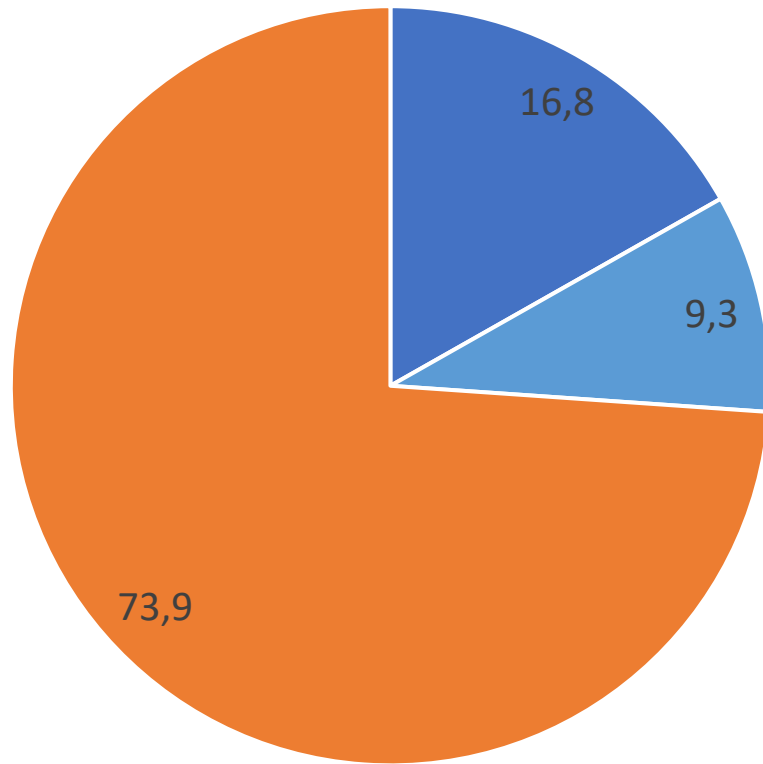
Revisión  
criterios  
consenso  
FPIES adultos

# Motivo remisión Alergología



# Evolución FPIES adultos

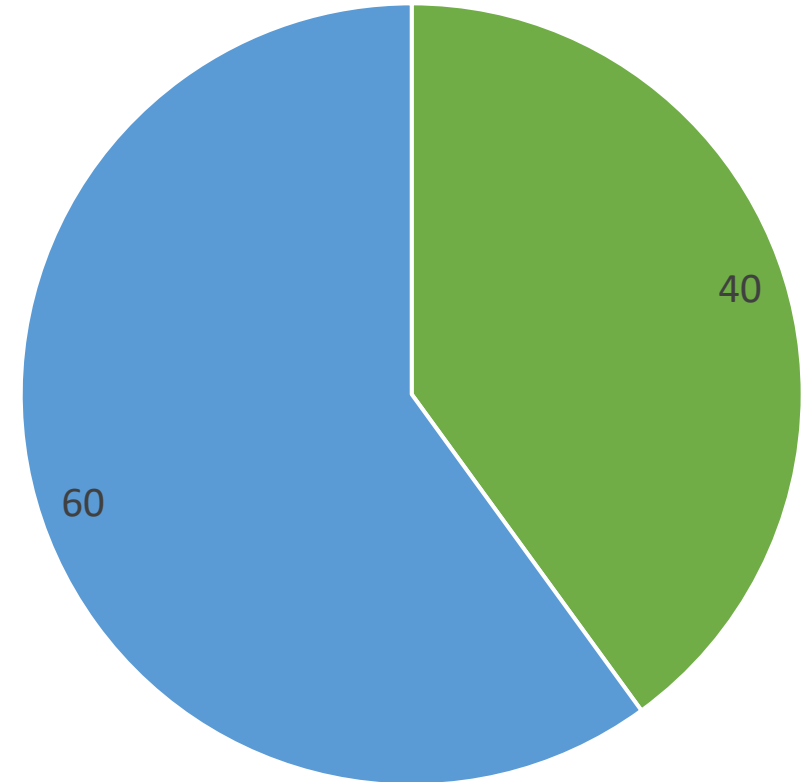
Seguimiento 6.2 años (IQR:1-10)



■ Tolerancia ■ Toler parcial ■ No toleran

Gonzalez-Delgado (2022)

Seguimiento 7 años (2-23)



■ Toleran ■ No toleran

S. Infante (2022)

# Egg-induced adult food protein-induced enterocolitis syndrome: Clinical phenotypes, natural history and immunological Characteristics.

**J ALLERGY CLIN IMMUNOL PRACT 2014 VOLUME 12, NUMBER 6**

Estudio prospectivo: (8 años)

30 Pacientes (27 mujeres)

**Fenotipos: no toleran trazas..... toleran diferentes presentaciones**

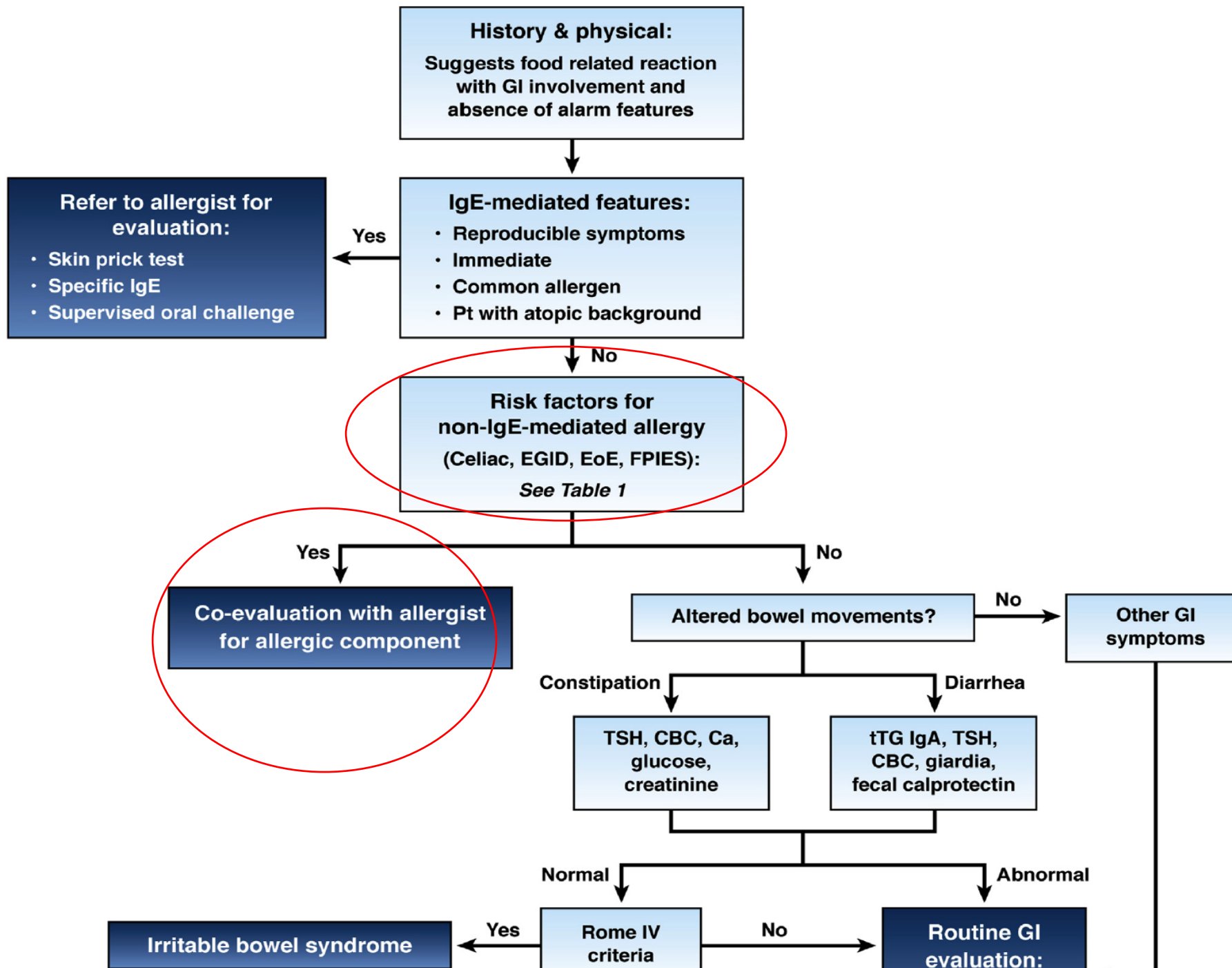
Procedencia: 40 % S. Digestivo (17 % pac: Dgo colon irritable, múltiples exploraciones )

Seguimiento 5 años  Resolución 17%, mejoría 10%

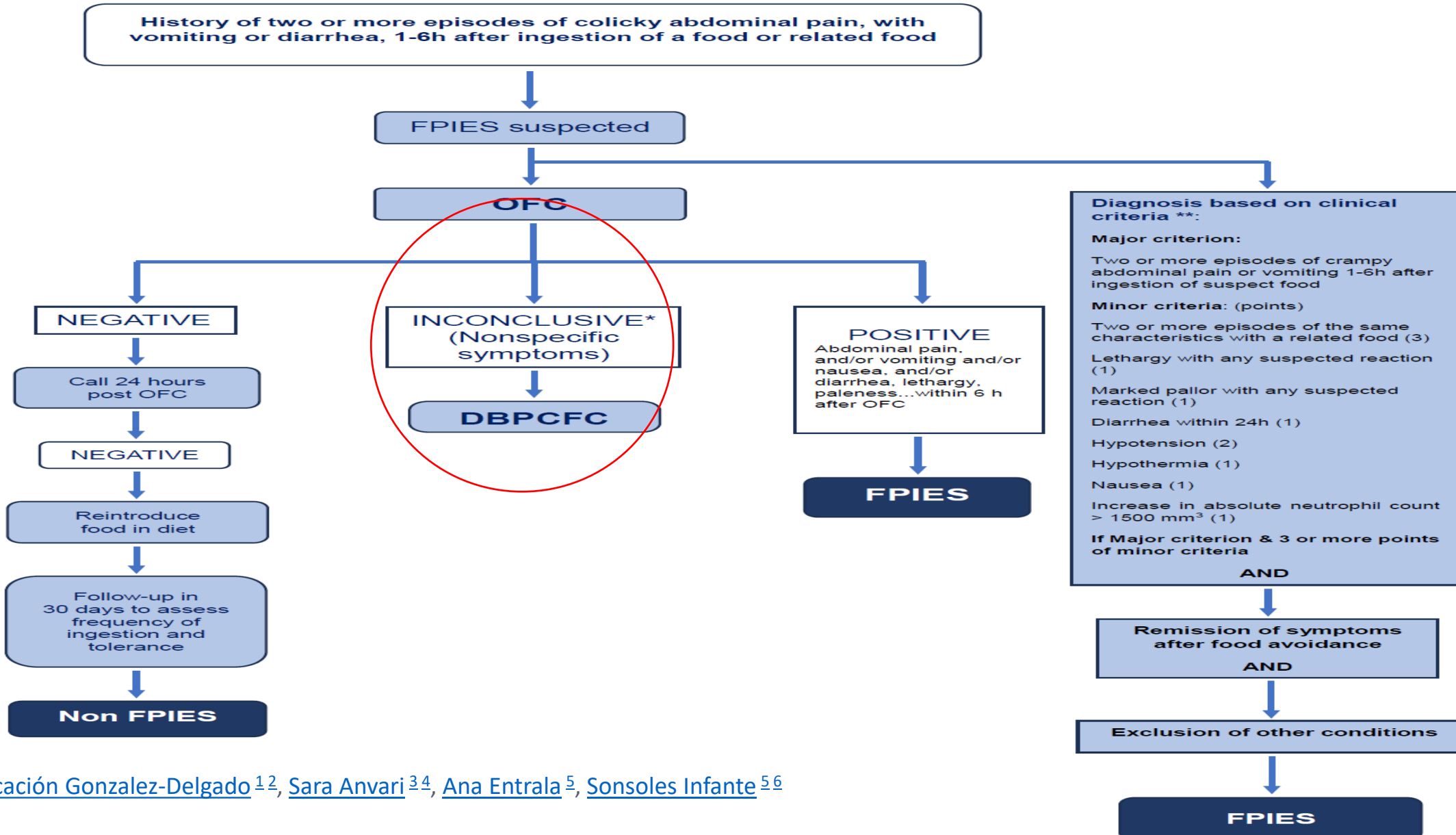
Alto índice de sospecha ( síntomas GI recurrentes tras ingesta alimentos con huevo)



*P Gonzalez-Delgado, MD, PhD S Anvari, MD, MS, J Barrachina, Ph, Al. Jimenez Portillo, MDe, Teodorikez Jimenez, MD, PhDa Francisco M. Marco de la Calle, MD, PhDe, and Javier Fernandez, MD, PhDa*







# Test de exposición controlada

## Objetivo:

Diagnóstico/ Resolución (12-18 meses tras la última reacción)

Centro hospitalario, Via ev (pro /con)

## Dosis ???

- Día 1 (30% ración) / Día 2 (70% ración)
- Un día (2 dosis )

Observación: 4 h de observación

## Criterios positividad

- Clínicos
- Neutrofilia
- PCR, calprotectina fecal ???



# Tratamiento

## Fase aguda

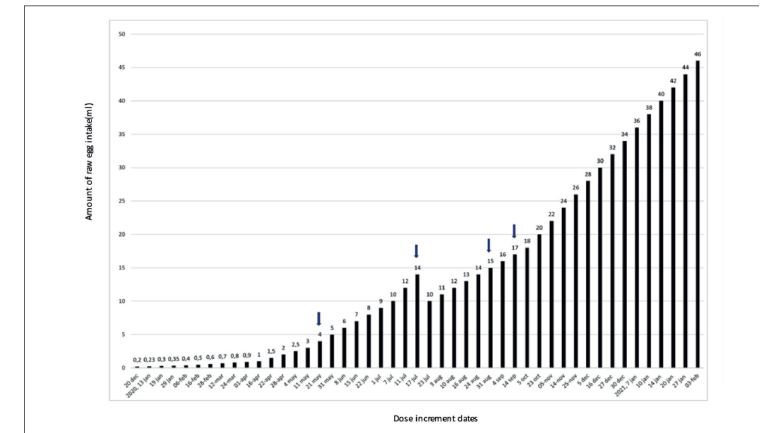
- Rehidratación oral, IV
- Ondansetron (6 m.) im, iv, oral
- Corticoides (FPIES severo) ?

## Seguimiento

- Evitar alimento implicado , relacionados (no)
- Reintroducción alimento tras periodo de evitación 2-3 años (OFC)
- Inducción tolerancia oral ??



Oral desensitization in egg acute food protein-induced enterocolitis syndrome



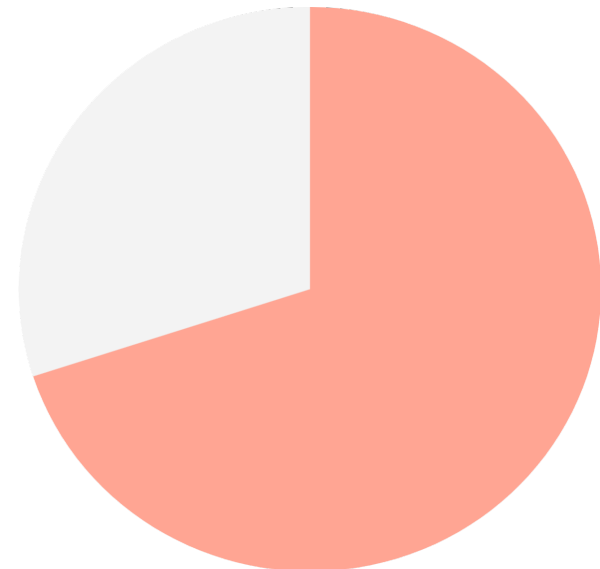
# Colon irritable y alimentos

Papel relevante alimentos, en colon irritable

Evitación alimentos, mejoría

- Efecto inmunológico?
- Reducción de otros ingredientes FODMAP,
- ATI (inhibidor tripsina amilasa)....?

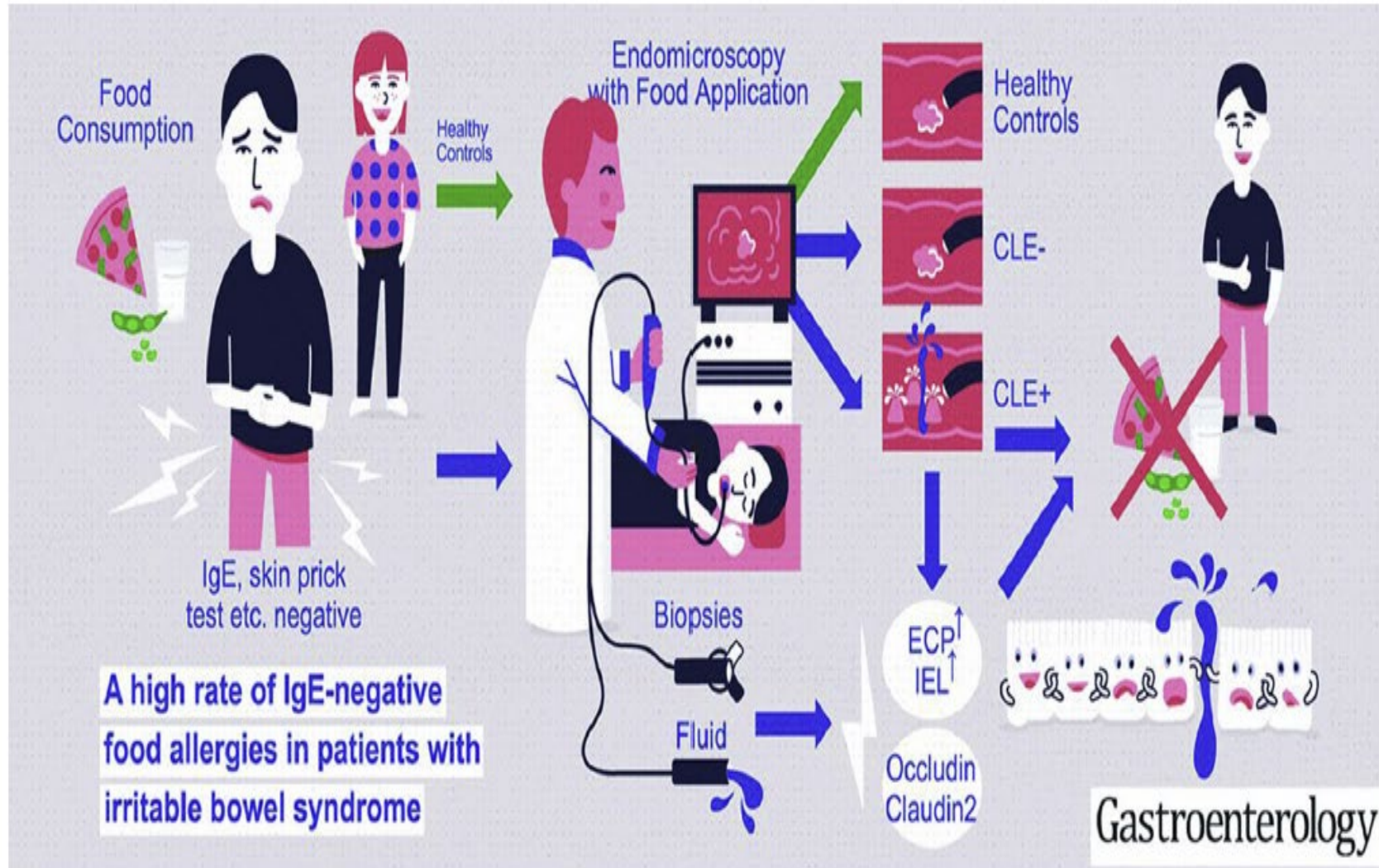
**Ausencia de biomarcadores fiables**



# Many Patients With Irritable Bowel Syndrome Have Atypical Food Allergies Not Associated With Immunoglobulin E



Annette Fritscher-Ravens,<sup>1</sup> Theresa Pflaum,<sup>1</sup> Marie Möisinger,<sup>1</sup> Zino Ruchay,<sup>1</sup> Christoph Röcken,<sup>2</sup> Peter J. Milla,<sup>3</sup> Melda Das,<sup>1</sup> Martina Böttner,<sup>4</sup> Thilo Wedel,<sup>4</sup> and Detlef Schuppan<sup>5,6</sup>



# Local immune response to food antigens drives meal-induced abdominal pain

<https://doi.org/10.1038/s41586-020-03118-2>

Received: 18 March 2020

Accepted: 27 November 2020

Published online: 13 January 2021

Check for updates

Javier Aguilera-Lizarraga<sup>1,2,2</sup>, Morgane V. Florens<sup>1,2,2</sup>, Maria Francesca Viola<sup>1</sup>, Piyush Jain<sup>1</sup>, Lisse Decraecker<sup>1</sup>, Iris Appeltans<sup>1</sup>, Maria Cuende-Estevez<sup>1</sup>, Naomi Fabre<sup>1</sup>, Kim Van Beek<sup>1</sup>, Elisa Perna<sup>1</sup>, Dafne Balemans<sup>1</sup>, Nathalie Stakenborg<sup>1</sup>, Stavroula Theofanous<sup>1</sup>, Goele Bosmans<sup>1</sup>, Stéphanie U. Mondelaers<sup>1</sup>, Gianluca Matteoli<sup>2</sup>, Sales Ibiza Martinez<sup>2,20</sup>, Cintya Lopez-Lopez<sup>3</sup>, Josue Jaramillo-Polanco<sup>3</sup>, Karel Talavera<sup>4</sup>, Yeranddy A. Alpizar<sup>5</sup>, Thorsten B. Feyerabend<sup>6</sup>, Hans-Reimer Rodewald<sup>6</sup>, Ricard Farre<sup>7</sup>, Frank A. Redegeld<sup>8</sup>, Jiyeon Si<sup>9,10</sup>, Jeroen Raes<sup>9,10</sup>, Christine Breynaert<sup>11</sup>, Rik Schrijvers<sup>11</sup>, Cédric Bosteels<sup>12,13</sup>

**Fig. 4 | Intramucosal injection of food antigens induces an immediate mucosal response in patients with IBS. a, b, Representative images**

